Amendments to the Drawings

The attached drawing sheet includes changes to Figure 13. This sheet, which includes Figure 13, replaces the original sheet that includes Figure 13. In Figure 13, previously omitted sequence ID numbers have been added.

REMARKS

At the time of issuance of the Office Action, claims 1-8 and 19 were pending. Applicants have amended claims 1, 2, 3, 4, 6, 8 and 19 and added new claims 20 - 37. Support for the amendments to the claims and for the new claims can be found in the claims and specification as filed.

Support for the amendment to claim 1 can be found, for example, at page 21, lines 22-27; page 30, lines 24-26; page 22, line 32 to page 23, line 14; and page 31, lines 2-6.

Support for the amendment to claim 2 can be found, for example, at page 24, lines 13-15 and page 28, lines 12-14.

Support for the amendment to claim 3 can be found, for example, at page 21, lines 22-27.

Claim 4 has been amended to provide for proper antecedent basis.

Support for the amendment to claim 6 can be found, for example, at page 34, lines 6-9; and page 40, line 26 to page 41, line 2.

Support for new claim 20 can be found, for example, at page 9, line 33 to page 10, line 1; and page 21, lines 19-27 and line 32.

Support for new claims 21-37 can be found, for example, at page 21, line 19 to page 22, line 8; page 21, line 32; page 26, Table I; page 30, lines 23-26; page 32, line 21 – 32, line 4; and page 47, lines 9-11.

The amendments to the drawing, the amendments to the claims, and the new claims, add no new matter. Accordingly, Applicants respectfully request entry of the amendments and new claims.

INTERVIEW

A telephone interview was conducted at Applicants' request between the Examiner and Tor Smeland and Scott Locke, attorneys for Applicants, on September 22, 2005. During the interview, attorneys for Applicants presented arguments against the rejections and discussed proposed amendments to certain claims, but no agreement was reached on claim language. Certain arguments presented to the Examiner are included herein in this Amendment and Reply.

OBJECTIONS TO THE SPECIFICATION

The Examiner requested that the term "SMARTscores," a trademark, be capitalized and accompanied by generic terminology wherever it appears. Applicants have amended the specification to comply with the Examiner's request, referring to "siRNA ranking(s)" where the term "SMARTSCORES" is employed. Applicants submit that inserting the term "siRNA ranking(s)" throughout the specification is not intended to overcome any rejection related to patentability, and Applicants submit that use of the term does not alter or in any way affect the scope of the subject matter of the specification, the scope or subject matter of the claims, or the meaning of any terms in the claims, specification, or drawings.

The Examiner also indicated that Figure 13 recites multiple nucleotide sequences not identified by SEQ. ID NOs. Applicants have amended the application to include SEQ. ID NOs in Figure 13 and provide a replacement drawing of Figure 13 that includes the omitted SEQ. ID NOs.

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

As noted above, Applicants have amended the drawings to include SEQ. ID NOs on the sequences disclosed in Figure 13, and submit a replacement drawing that includes the SEQ. ID NOs of the sequences disclosed in Figure 13.

Applicants note that they previously complied with all sequence listing requirements by their prior submission of June 29, 2004. However, in compliance with the requirement for this application that has been made special, Applicants also transmit herewith a Reply to Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures. The Reply comprises a CD-ROM copy of the sequence listing, submitted in lieu of a paper copy under 37 C.F.R. §§ 1.52(e) & 1.823, a CRF copy of the sequence listing on CD-ROM, and a statement that the paper copy and the CRF copy are identical to one another, and that the submitted CRF copy and paper copy of the sequence listing on CD-ROM are identical to the previously filed CRF copy and paper copy of the sequence listing on CD-ROM. Applicants submit that the Reply is fully responsive to the Notice to Comply.

REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1-5 as incomplete for allegedly omitting essential steps so as to amount to a gap between steps. The Examiner asserted that the missing steps were (c) a comparison between the result determined for functionality as set forth in step (b) and a set standard previously determined as a criterion for selecting a desired siRNA; and selection of an siRNA based on the siRNA meeting the established criterion of step (c). Applicants respectfully disagree that essential steps have been omitted and request reconsideration and withdrawal of the rejection in view of claim 1 as amended.

With respect to the allegedly missing step of a comparison between the result determined for functionality and a set standard previously determined for functionality, Applicants note that the method is inventive regardless of the particular functionality that is sought by a particular user, and thus is not dependent on a functionality level. Instead, the method allows for selecting rationally designed siRNA that would have better (or worse) silencing capabilities based on the presence or absence of a particular base at a particular position relative to the same siRNA that did not satisfy the at least one criterion. Accordingly, Applicants have deleted the reference to functionality. Applicants also direct the Examiner to page 21, lines 19 – 27 of the specification, which describes the meaning of the phrase "rational design" as increasing the probability that an siRNA will be functional.

With respect to the allegedly missing step of selecting an siRNA, Applicants have added step (c), which recites selecting the rationally designed siRNA.

Accordingly, Applicants submit that this rejection should be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Examiner rejected claim 19 as allegedly failing to comply with the written description requirement. She asserted that the at least two siRNA molecules of the kit must be identified by further experimentation, and that the specification would not allow a person of ordinary skill in the art to predict the structures of the claimed siRNAs. Applicants respectfully disagree.

To fulfill the written description requirement, a specification must describe an invention in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention. *Reagents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997), *cert. denied,* 523 U.S. 1089 (1998). The Examiner is burdened with presenting evidence or reasons why a person of ordinary

skill in the art would not recognize in the disclosure a description of the invention as claimed. *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976); *see also*, Interim Guidelines for the Examination of Patent Applications Under The 35 U.S.C. 112 ¶ 1 "Written Description" Requirement, 66 Fed. Reg. 1099-1111, 1105 (2001) ("rejection of an original claim for lack of written description should be rare").

Applicants respectfully submit that the Examiner has not met the burden of presenting a *prima facie* case of lack of written description. Applicants submit that the Examiner has not presented sufficient evidence or provided sufficient reason as to why a person of ordinary skill would not recognize in the disclosure a description of a kit as claimed.

But assuming solely for the sake of argument that the Examiner has articulated a *prima facie* case of lack of written description, Applicants submit that claim 19 amply satisfies the written description requirement.

First, Applicants have not claimed the kit by functional characteristics uncorrelated with structure. Instead, Applicants have claimed siRNA with specific, precise structural limitations dictated by application of the recited formulas. In contrast to the Examiner's assertions, claim 19 recites no functional limitations that are not dictated by the claimed structural limitations on the kit components. Claim 19 requires only that the kit components be selected according to the applied formula(s). The formulas describe ***structural*** limitations—not functional limitations that exist independent of structure. Accordingly, claim 19 comprises ample structural limitations on the siRNAs of the kit to comply with 35 U.S.C. § 112.

Second, Applicants have amply demonstrated that they possessed the invention of claim 19 and that it is ready for patenting. Possession of an invention can be shown by an actual reduction to practice, showing that the invention was ready for patenting by providing a disclosure having drawings or structures that show the invention was

complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the invention. *Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55 (1998), *reh'g denied,* 525 U.S. 1094 (1999). An invention need only be described with "sufficient clearness and precision to enable those skilled in the matter to produce [it]." 525 U.S. at 63 (citations and internal quotes omitted).

The *Pfaff* case supports Applicants' contention that the invention of claim 19 was ready for patenting, since claim 19 is directed to an invention that is described in the specification with sufficient clearness and precision to enable a person of skill in the art to construct a kit according to the claim. The standard in *Pfaff* is met by claim 19 because person of ordinary skill in the art would be able to construct the claimed kit by applying any one of the recited formulas of claim 19 to a gene database, a gene, or a gene fragment of interest. A person of ordinary skill applying the formula would obtain at least two siRNA that are optimized according to a claimed formula, where the at least two siRNA bear the structural limitations imposed by the selected formula.

Moreover, the specification discloses a plurality of siRNA sequences selected using Formulas VIII and IX (see, for example, Table V (pages 70-73). Well over a million sequences selected by applying Formula VIII to the online NCBI REFSEQ database have been provided in the specification (see, for example, the specification as filed at page 73, line 4 to page 75, line 9; and Tables XII-XV, submitted on CD-ROM). And almost two thousand examples are provided in Tables VI-X and on pages 146-153 and 156. Thus, claim 19 recites a kit that is described with sufficient clarity and precision to enable a person of skill in the art to make the kit. No guesswork by a person of ordinary skill is required for an accurate and precise reading of claim 19. No experimentation is required to arrive at the claimed kit. No ambiguity exists as to what is claimed. Accordingly, Applicants request reconsideration and withdrawal of the written description rejection.

REJECTIONS UNDER 35 U.S.C. § 101

The Examiner rejected claims 1 - 2, and 6 - 8 as allegedly being directed to non-statutory subject matter. She asserted that the claimed methods are not limited to a practical application of the recited mathematical algorithms of Formulas I-VII, and that the claims recite no limitation clearly defining a practical use of the siRNAs, nor how a functionality measure is used to establish the basis upon which an siRNA can be selected.

Applicants respectfully disagree with the Examiner, and in light of the amendments above, Applicants submit that this rejection is moot. Step (c) of amended claim 1 recites selecting a rationally designed siRNA and as the use of the phrase "rationally designed" denotes, the method may be used to increase the probability of identifying a functional or hyperfunctional siRNA. Claim 2 depends on claim 1, and thus for at least the reasons that claim 1 satisfies 35 U.S.C. § 101, so too does claim 2. A utility of these methods is that they enable the more efficient selection of an siRNA that will silence a target than random selection of an siRNA would provide.

Amended claim 6 also satisfies 35 U.S.C. § 101. The Examiner rejects this claim, asserting that it like the other rejected claims, is directed to a method of selecting siRNA. However, Applicants respectfully submit that the Examiner may not have appreciated that claim 6 is directed to a method for developing an algorithm. The practical application of this claim is noted in the preamble; it allows development of a formula that enables selection of siRNA that are capable of silencing a target gene. With an algorithm, one may be able to avoid subsequent trial and error procedures to determine, which of a set of siRNA would have the best level of silencing.

Applicants have canceled claim 7.

With respect to claim 8, Applicants have amended the claim to depend on claim 1, and included in the claim language an indication of how to measure hyperfunctionality.

Applicants direct the Examiner to page 14, lines 17 –35 of the specification for support for this amendment and a further recitation of meanings of the terms "functional" are recited in the specification. A utility of the invention is that it allows for the selection of particularly potent siRNA.

Regarding the Examiner's position that the claims include no instruction as to how a measure of functionality is used for selection, Applicants submit that the utility of the rejected claims does not depend on specific levels of functionality. Rather, the claimed methods provide a person of ordinary skill the ability to rationally design and select an siRNA directed against a target gene using non-target specific criteria, for the purpose of silencing the target gene.

In light of the above, Applicants request reconsideration and withdrawal of the rejections based on 35 U.S.C. § 101.

REJECTIONS UNDER 35 U.S.C. § 102(E)

The Examiner rejected claims 1 and 19 as allegedly anticipated by U.S. Patent Application Publication No. 2004/0054155 by Woolf ("Woolf"). The Examiner asserted that Woolf discloses considering GC content and Tm of oligonucleotides when selecting dsRNA for inhibiting gene expression.

Applicants respectfully disagree with the Examiner and submit that Woolf does not anticipate the inventions of claim 1 and 19. With respect to claim 1, Applicants have amended the claim to recite that application of at least one non-target specific criterion which is the presence or absence of a particular nucleotide at at least one of sequence positions 1-19 (see specification at page 22, line 32 – page 23, line 14). The Examiner has not pointed to any portion of Woolf that teaches, discloses or otherwise suggests such limitations. Thus, claim 1 is patentable over the cited art.

Regarding claim 19, Applicants respectfully submit that the Examiner has not shown how—within any of the sets of oligonucleotides disclosed by Woolf—at least two of the sequences would be the two most functional 19 –25-mers (as defined by the recited formulas) of for a given target gene. See, for example, page 33, lines 6 –18 of Applicants' specification. Further, the Examiner has not indicated where, in Woolf, a kit comprising at least two optimized siRNA is disclosed, wherein the optimized siRNA are selected according to the recited formulas. Woolf does not disclose, teach, or suggest any kits comprising optimized siRNAs that meet the structural requirements of the recited formulas in accordance with the invention.

Further, Applicants' new claims 20-33 are also patentable in light of the cited reference. Woolf does not disclose, teach, or suggest non-target specific criteria that comprise the presence or absence of an A at position 19 as recited in new claim 20; or the method of claim 1 employing at least two to four candidate siRNA (claims 21-24); the variables recited in claim 24-30; nor rationally designed siRNA in accordance with claim 1 having the recited functionalities of claims 31-33.

Accordingly, Applicants respectfully submit that the presently pending claims are patentable in light of the Woolf reference, and request reconsideration and withdrawal of the rejections based on Woolf.

DOUBLE PATENTING

The Examiner provisionally rejected claim 1 under the judicially created doctrine of obviousness-type double patenting over claim 7 of U.S. Patent Application Serial No. 10/745,395, published as U.S. 2004/0248299 ("Jayasena"). She asserted that claim 7 of Jayasena represents a species of the broad genus method recited in rejected claim 1.

Applicants have amended claim 1, and thus submit that the double patenting rejection is no longer applicable. More specifically, Applicants note that currently amended claim 1 recites the application of at least one non-specific criterion that comprises the presence or absence of a nucleotide at a particular position. The Examiner has not suggested that the cited reference recites this limitation. Thus, Applicants submit that the rejection is now moot.

Applicants also note two points. First, the priority date of Jayasena (December 27, 2002), is after the priority date of the instant application (November 14, 2002). Second, the Jayasena application and the instant application are assigned to different assignees. Drs. Khvorova and Reynolds, named inventors on both the cited reference and the present application, were employees of Amgen until approximately August 2002, and no later than September 2002, Drs. Khvorova and Reynolds became employees of Dharmacon, Inc., the assignee of the instant application. Thus, at the time of the filing of the priority documents, Drs. Khvorova and Reynolds were employed by Dharmacon, Inc.

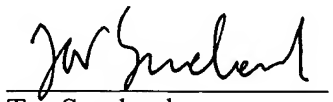
Conclusion

All of the Examiner's rejections having been fully traversed and addressed, Applicants respectfully request allowance of the pending claims.

Applicants enclose a fee transmittal authorizing a charge to our deposit account in the amount of $250.00 to cover the additional dependent claims. Eighteen new claims have been added, but 13 have been canceled. Accordingly, Applicants submit that fees for only 5 additional claims are needed. No other fee is believed to be required in connection with the filing of this Amendment and Reply. If any fee is deemed necessary, or overpayment has been made, please charge, or credit, Deposit Account No. 11-0171.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,



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